

Chloroquine resistance in Pakistan and the upsurge of falciparum malaria in Pakistani and Afghan refugee populations

By I. SHAH*, M. ROWLAND†‡, P. MEHMOOD*, C. MUJAHID§, F. RAZIQUE¶, S. HEWITT† AND N. DURRANI†

* *National Institute of Malaria Research and Training, Lahore, Pakistan*

† *HealthNet International, P.O. Box 889, Peshawar, Pakistan*

§ *Directorate of Malaria Control, Islamabad, Pakistan*

¶ *North West Frontier Department of Malaria Control, Peshawar, Pakistan*

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Surveys conducted in Pakistan during the last decade show that falciparum malaria has become resistant to chloroquine in Pakistani and Afghan refugee populations throughout the country. Although RI resistance is common everywhere (with a frequency of 30%–84%), RII is rarer (2%–36%), and RIII resistance has yet to be detected. The national policy is to prescribe chloroquine as first-line treatment of malaria. A repeated in-vivo survey in a sentinel village indicated that prescription of chloroquine can lead to a 15% increase in the frequency of resistance in a single year, and similar trends were observed in other districts.

Coinciding with the spread of resistance is a 6-fold increase in the number of falciparum cases recorded nationally between 1982 and 1992 and a parallel, 5-fold increase in the number of cases recorded in the Afghan refugee population. Resistance contributes to this trend in various ways. Firstly, patients with resistant malaria make repeated visits to health centres. In the sentinel village, for example, where resistance was measured at 71%, recrudescence inflated by 66% the genuine incidence of new infections recorded at the health centre. Secondly, owing to ineffective treatment, resistant infections are often still patent during the post-transmission season. This may enlarge the 'overwintering' parasite reservoir, leading to a surge of new cases when transmission resumes. Other factors potentially contributing to the upsurge in falciparum include the decreased availability of insecticide for indoor spraying.

Despite the problems posed by resistance for case management, the evidence from the vector-control programme among the refugees is that malaria control through well-targeted campaigns of insecticide spraying is still able to reduce the incidence of falciparum malaria to a level that existed before the advent of resistance.

Transmission of vivax and falciparum malaria in Pakistan is seasonal, and mostly occurs in the second half of the year after the July–August monsoon (Strickland *et al.*, 1987; Rowland *et al.*, 1997b). A discernible trend in Pakistan is for malaria to show long-term periodic cycles, the last major epidemic having occurred in the mid-1970s (Zulueta *et al.*,

1980). Falciparum malaria is particularly unstable at the northern end of its range, and can fluctuate markedly from year to year depending on climatic variation. High rainfall in autumn and temperatures above average in November and December are notable risk factors that can enhance or prolong the transmission season, a perceptible trend in recent years (Bouma, 1995). Compounding the problem is the development of chloroquine resistance, which was first reported in Pakistan in

* Author to whom correspondence should be addressed.
E-mail: malaria@msfhn.psw.erum.com.pk; fax: + 92 521 840379.

1984 (Robinson *et al.*, 1984; Fox *et al.*, 1985). Many areas of the country have now been surveyed using the extended in-vivo test recommended by the World Health Organization (WHO). The results of these surveys, discussed below, show that resistance is widespread in the country. The incidence of falciparum malaria, as recorded by malaria-control programmes among Pakistani and Afghan refugees, appears to be increasing. The ways in which chloroquine resistance may be contributing to this upsurge were investigated in the present study by examining records of falciparum on a 'micro' level, in indicator villages, and on a 'macro' level, in different provinces of the country. The possible contributions to the upsurge made by operational changes to the national control programme, such as the decline in vector-control activities, were also examined. Finally, the significance of chloroquine resistance as an obstacle to the control of falciparum malaria in Pakistan was assessed.

SUBJECTS AND METHODS

Surveys of In-vivo Resistance

To record the spread of chloroquine-resistant *Plasmodium falciparum*, in-vivo surveys, using the WHO extended field test, have been carried out each year since 1977 by staff of the National Institute of Malaria Research and Training (NIMRT). With the limited manpower available, surveys had to be restricted to different parts of the country in different years. Subjects have included Afghan refugee communities. Some sites were re-surveyed after one or more years. Under NIMRT's supervision, surveys have also been carried out by Provincial Malaria Control Departments and by HealthNet International (HNI), a non-governmental organization involved in malaria control in Afghan refugee settlements. Standard WHO methodology was always used (WHO, 1973). Enrollment criteria were a parasitaemia of 1000–80 000 asexual parasites/ μ l blood, and no recent intake of chloroquine, as indicated by Dill–Glazko urine tests. Infected individuals were selected at random. Thick

and thin films were prepared and Giemsa-stained immediately before treatment with chloroquine and at 1–3-day intervals thereafter. The number of asexual parasites/200 leucocytes was counted. A smear was regarded as negative if 200 thick-film fields failed to show the presence of asexual parasites. Chloroquine tablets, specially prepared for in-vivo studies, were provided by WHO. Tablets were administered in divided doses over 3 days to give a total dose of 25 mg/kg body-weight. All doses were given under supervision. Whenever conditions were suitable, at least 50 cases were enrolled per test. The mean number enrolled was 43, with a range of 15–67.

Epidemiological Studies on Afghan Refugees

The presence of Afghan refugees living in compact villages, served by a basic health unit (BHU) offering free medical services, provided an ideal opportunity to study the presentation and recurrence of resistant infections through a process of passive case detection (PCD). In 1991, 10% of families of two highly malarious villages, Baghicha and Kagan (with a total combined population of 13 920), in Mardan district of the North West Frontier province (NWFP), were selected at random and issued with BHU registration cards distinct from the norm. The selected families received no special treatment at the BHU but whenever family members presented with fever, details were recorded in a separate register that facilitated data entry and analysis. The standard procedure for patients showing possible symptoms of malaria was to take a thick and thin blood smear, give presumptive treatment with chloroquine, and to examine the slides within 24 h. Confirmed cases were treated with 25 mg chloroquine/kg bodyweight in divided doses over 3 days. Cases of vivax malaria were given an additional, 5-day course of primaquine (0.25 mg/kg daily). Recrudescing falciparum infections were retreated with a 5-day extended course of chloroquine (40 mg chloroquine/kg) or with sulphadoxine–pyrimethamine.

A survey of malaria prevalence among the selected families was carried out in late December, during the post-transmission season, to assess the success of the earlier drug treatments. Families were visited in their homes and blood smears were taken from all willing members.

Also in December, inhabitants of Baghicha were subjected to a survey of in-vivo chloroquine resistance, conducted by staff of NIMRT. Exactly 1 year later, a follow-up, in-vivo survey was carried out, this time by HNI.

National and Refugee Malaria Statistics

Government-run rural health centres and BHU provide free medical services for the local Pakistani population and are comparable with the BHU in the refugee camps. The Provincial Departments of Malaria Control compile the malaria-case records from these facilities and earmark the localities where incidence is high for focal spraying with residual insecticide the following year. The United Nations High Commission for Refugees (UNHCR) is responsible for malaria control in the Afghan refugee villages, and adopts the policy of the national malaria-control programme (MCP), but delegates responsibility for data collection, analysis and planning to HNI. Annual malaria data for the last one or two decades are re-analysed here to show trends in falciparum incidence, slide-positivity rates (SPR), and falciparum:vivax ratios.

RESULTS

In-vivo Resistance Surveys

The consolidated results of 20 years work are presented in Fig. 1. Resistance was first detected in 1981 in Sheikhpura in the Punjab (Figs 1 and 2). Surveys 2–3 years later in other districts showed that RI resistance was becoming widespread in the Punjab and increasing in frequency. RII resistance was comparatively rare at that time, occurring in only a few percent of cases and in only two of the five districts surveyed. In 1985 resistance was recorded in NWFP. Over the next decade RII

resistance increased in frequency, reaching a national maximum of 36% in Mianwali on the Punjab–NWFP border in 1992. Only one survey was ever carried out in Balochistan province, and this showed a resistance frequency of 52%. Some localities were re-surveyed after an interval of several years: in Sheikhpura resistance increased from 3% to 37% between 1981 and 1990; in Mardan (NWFP) it increased from 64% to 94% between 1985 and 1987; and in Bannu (NWFP) it increased from 56% to 92% between 1986 and 1992. Afghan refugee villages showed levels of resistance similar to those in Pakistani villages. Despite the increase in frequency of RII resistance in recent years, no case of RIII resistance has yet been recorded in Pakistan.

Studies on Afghan refugees

According to BHU records, 10% (138/1392) of refugees in Baghicha and Kagan contracted falciparum malaria between July and December 1991 (Fig. 3). Of these cases, 49% (68/138) recurred once and 17% (23/138) recurred again, producing an overall incidence of 16% (229/1392) for the 6-month period. The mean interval between recurrences was 18 days. If chloroquine resistance was absent from these villages, the probability of a successfully treated patient contracting a new infection of falciparum would be around 10% (approximately 13/138) or five times less than the observed frequency of first recurrences. An in-vivo survey conducted in December revealed that 71% of falciparum cases in Baghicha were, in fact, chloroquine-resistant (Fig. 1). Thus one of the effects of resistance at the observed frequency was to inflate the reported incidence of falciparum by 66% over the period of observation, from the predicted 11% should resistance not have been present [i.e. (138 + 13)/1392] to 16% (229/1392). In contrast, the proportion of the population presenting with vivax malaria was, at 22% (310/1392), double that which presented with falciparum, and yet only 25% (77/310) of these infections recurred after treatment and only 1% (5/310) recurred a second time (Fig. 3). If the proportion of the population that becomes re-infected with vivax is assumed to

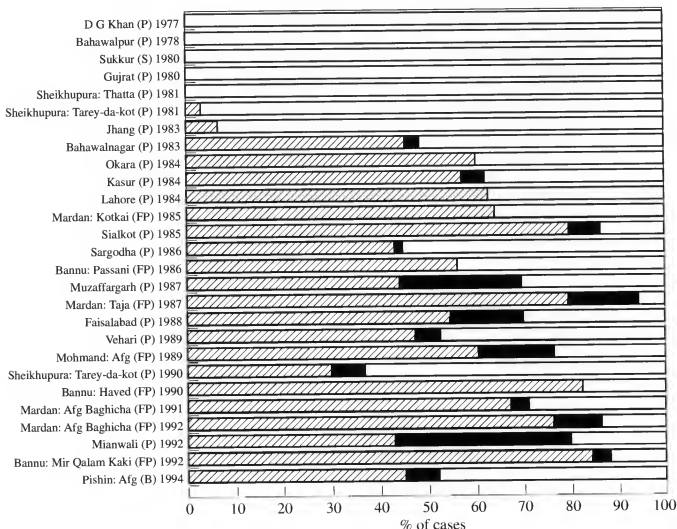


Fig. 1. Consolidated results of the surveys of in-vivo chloroquine resistance undertaken in Pakistan since 1977. Infections with parasites which were resistant at the RI level (▨) or RII level (■) or susceptible (□) were found. The vertical axis records the district, the village (if the district had been surveyed more than once), the province [Punjab (P), Sind (S), North West Frontier province (FP), or Balochistan (B)] and the year of survey. Afg, Surveys in Afghan refugee villages.

be the square of the proportion infected once, then the result, 5.0%, turns out to be not significantly different from the observed 5.5% (77/1392) for second attacks. This suggests that most second attacks with *P. vivax* were new infections rather than relapses.

Almost 80% (1107/1392) of the selected group of refugees were willing to participate in the prevalence survey in December. Of this group, 6% (70/1107) were falciparum positive and 9% (98/1107) were vivax positive during the survey. Of the survey members who had been previously diagnosed as falciparum-positive by PCD at the BHU, 32% (41/128) were still positive during the prevalence survey. In

contrast, only 8% (22/280) of vivax cases diagnosed by PCD were still positive during the survey ($\chi^2 = 37$; one degree of freedom; $P < 0.001$). Of the falciparum patients who had presented their infections just once at the BHU, only 25% (16/64) were still falciparum-positive during the survey. A much higher proportion [41% (26/64)] of the falciparum patients who repeatedly attended the BHU with recurrent infections was still positive during the prevalence survey. This suggests that resistant infections were more likely to be patent during the post-transmission period than susceptible infections, and that repeated treatment with chloroquine was

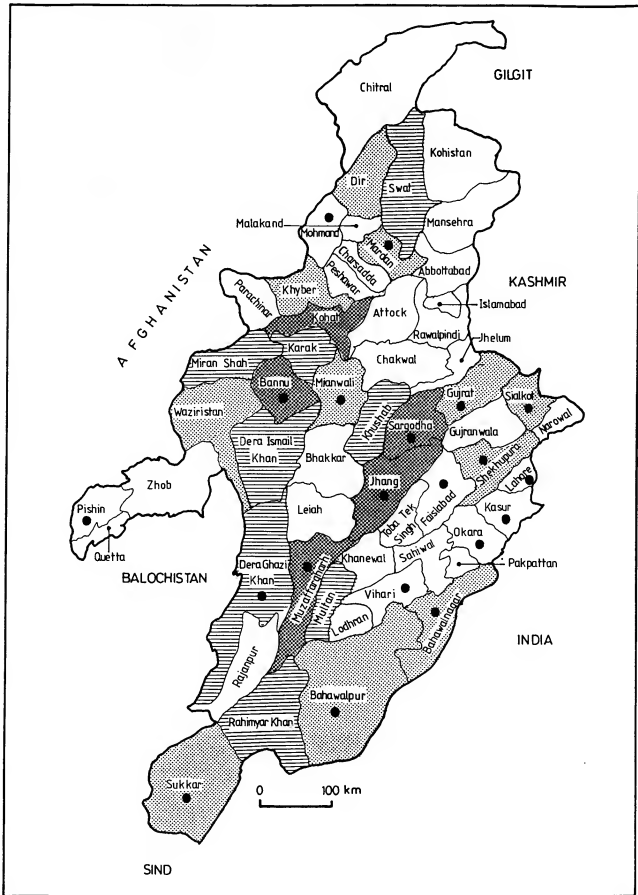


Fig. 2. Map of Pakistan showing districts where surveys of in-vivo chloroquine resistance have been carried out (●) and malaria endemicity in 1992, at levels of < 1000 (□), 1000–1999 (▨), 2000–2999 (▧) or > 3000 (▩) cases/year in each district.

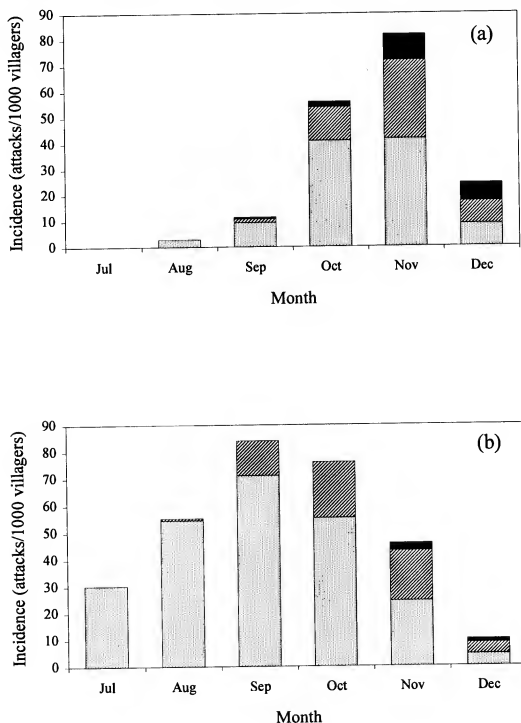


Fig. 3. The incidence of first (□) and recurrent second (▨) and third (■) attacks with falciparum (a) and vivax (b) malaria in two neighbouring refugee villages in Mardan district in 1991.

prolonging the selection pressure on resistance. This interpretation is supported by the result of a follow-up, in-vivo survey in December 1992; within a year, resistance had increased from 71% to 86% (Fig. 1).

Presentation rates for falciparum cases at the BHU were higher than for vivax cases. Only 24% (22/93) of the vivax cases in the

prevalence survey had had their infections diagnosed by PCD at the BHU. In contrast, 63% (41/65) of the survey's falciparum cases had been diagnosed previously at the BHU. It is clear that a high proportion of all malaria infections, but of vivax in particular, were going undiagnosed and untreated or being diagnosed elsewhere. During interviews with

HNI, 92% of refugee families claimed to use the village BHU in preference to private clinics; these claims cannot be confirmed, but it was certainly the case that private clinics and pharmacies were not permitted within the refugee villages. It seems likely that many cases were clinically asymptomatic, particularly those of vivax malaria. The difference in presentation rate between vivax and falciparum cases ($\chi^2 = 27$; one degree of freedom; $P < 0.001$) may be attributable to the greater severity of falciparum's clinical symptoms. Interviews held during the prevalence survey revealed that only 4% (4/98) of vivax cases and 23% (16/70) of falciparum cases were symptomatic at the close of the transmission season (symptomatic patients were defined as those who complained of recent fever, body pain, headache and vomiting). While these actual values may not represent the clinical situation existing during the height of the transmission season, the relative values support the proposed explanation for the difference in presentation rate between vivax and falciparum.

National Records on Malaria in Pakistan

Since the late 1970s there has been a gradual increase in the number of recorded cases of falciparum in the Pakistani population; only 3630 cases were recorded in 1980 but this increased to 56 885 in 1992, even though similar numbers of slides had been examined each year (3 006 624 in 1980 and 2 692 135 in 1992). An increase in the number of falciparum cases has also been observed in the Afghan refugee population, from only 7572 recorded cases in 1987 to 38 359 in 1992. These trends are presented in Fig. 4(a) as changes in annual falciparum SPR. An alternative presentation, expressed in terms of annual falciparum incidence, was not favoured since this would require an accurate estimate of population size, and this was not available for the Pakistani population. Use of SPR as an indicator is not wholly reliable either, because over the last decade there has been a gradual switch from active case detection (ACD) to passive in Pakistan (from 12% PCD in 1982 to 25% PCD in 1991) and PCD tends to pro-

duce higher SPR. This potentially confounding factor can be circumvented by presenting the falciparum data with reference to vivax data, since *P. falciparum* and *P. vivax* would be equally affected by the switch from ACD to PCD. Falciparum malaria is therefore shown as a percentage of all malaria (%falciparum) in Fig. 4(b). Data for the Punjab are presented separately from data for the rest of Pakistan because the Punjab was subject to a major epidemic in the mid-1970s, which distorts the pattern observed in the rest of the country.

Linear regression was used to analyse the changes in falciparum SPR and %falciparum over time. The results (see Table) reveal a significant increase in both falciparum SPR and %falciparum in every province except the Punjab. However, if the data collected from the Punjab from 1980 onwards (i.e. after the epidemic in the 1970s) are analysed, a positive correlation, similar to that in the rest of the country, emerges. To test whether the upsurge in falciparum was an artifact caused by the switch from ACD to PCD in the national control programme, the ACD and PCD datasets were analysed separately. The two methods of case detection showed nearly identical rates of increasing %falciparum with time, and both showed significant increases in falciparum SPR with time (see Table). The upsurge was therefore not an artifact caused by programme reform. The falciparum SPR and %falciparum in the Afghan refugee population show a positive correlation over time, similar to that in the Pakistani population (see Table).

Figure 4 shows that the upsurge in falciparum started in the early to mid-1980s, around the same time that chloroquine resistance was becoming widespread in Pakistan. Falciparum SPR increased about 10-fold from 0.5% to around 5% during the next decade [Fig. 4(a)]. Falciparum as a percentage of all malaria increased 5-fold, from 10% to 50% in the Pakistani population and from 5% to 25% in the refugee population [Fig. 4(b)]. While this trend still continues in the local population, the number of falciparum cases in the refugee population has decreased dramatically

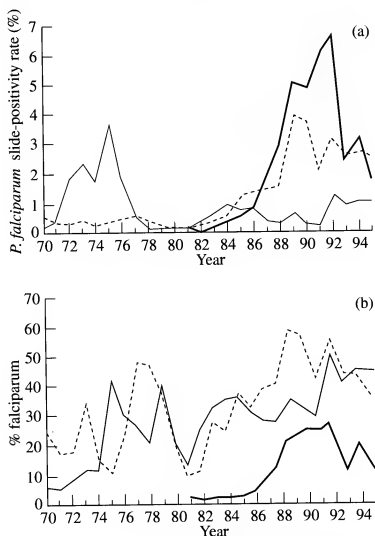


Fig. 4. The trends since 1970 in *P. falciparum* slide-positivity rates (a) and *P. falciparum* infections as a percentage of all malaria-positive slides (b) among refugees (—), subjects from North West Frontier province, Sind or Balochistan (---) and subjects from the Punjab (....).

over the last few years (from 41 049 cases in 1991 to 4804 cases in 1995), mainly as a result of vector control through indoor spraying with malathion and lambdacyhalothrin. The spraying campaigns started in 1991, when 36% of camps (representing 845 000 refugees) were sprayed. By 1995, the reduction in falciparum was such that only 22% of camps (289 000 refugees) still needed spraying. The reduction in falciparum is reflected in a decrease in SPR after 1992 [Fig. 4(a)].

The consumption of insecticide by the Pakistan MCP is illustrated in Fig. 5. Various insecticides have been used during the last three decades. Malathion was the only insecticide used in significant amounts during the mid-1980s when falciparum began its upsurge,

even though use of insecticide was then actually increasing. On the basis of this information, responsibility for the upsurge cannot be levelled at impaired vector control brought about by lack of resources. Only from 1987 did malathion consumption decrease, and this coincided with a further increase in falciparum malaria.

DISCUSSION

Since the mid-1980s chloroquine-resistant falciparum malaria has become widespread in the Punjab, NWFP, and in the parts of Balochistan surveyed. From the limited number of in-vivo surveys carried out, its spread seems fairly rapid. The frequency of resistance con-

TABLE Results of regression analyses on <i>Plasmodium falciparum</i> slide-positivity rates (SPR) and the proportions of all malaria cases attributed to <i>P. falciparum</i> (% <i>falciparum</i>) against time										
Sample	Period	<i>P. falciparum</i> SPR				% <i>falciparum</i>				df, Degrees of freedom.
		Slope	S.E.	F-value and (df)	P	Slope	S.E.	F-value and (df)	P	
Punjab	1970-1995	-0.27	0.22	1.6 (1, 24)	> 0.05	1.31	0.23	32.3 (1, 24)	< 0.0001	
Punjab	1980-1995	0.45	0.17	13.0 (1, 16)	< 0.01	0.85	0.21	15.7 (1, 24)	< 0.001	
North West Frontier province	1970-1995	0.80	0.13	40.1 (1, 24)	< 0.0001	1.88	0.26	50.7 (1, 24)	< 0.0001	
Sind	1970-1995	1.49	0.30	25.1 (1, 24)	< 0.0001	0.83	0.39	4.7 (1, 24)	< 0.05	
Balochistan	1970-1995	1.72	0.35	24.6 (1, 24)	< 0.0001	1.70	0.40	17.6 (1, 13)	< 0.001	
Afghan refugees	1981-1995	3.36	1.60	10.0 (1, 13)	< 0.01	1.45	0.28	26.9 (1, 18)	< 0.0001	
Active case detection	1975-1995	0.55	0.08	49.9 (1, 18)	< 0.0001	1.37	0.30	20.6 (1, 18)	< 0.0001	
Passive case detection	1975-1995	1.60	0.32	25.6 (1, 18)	< 0.0001					

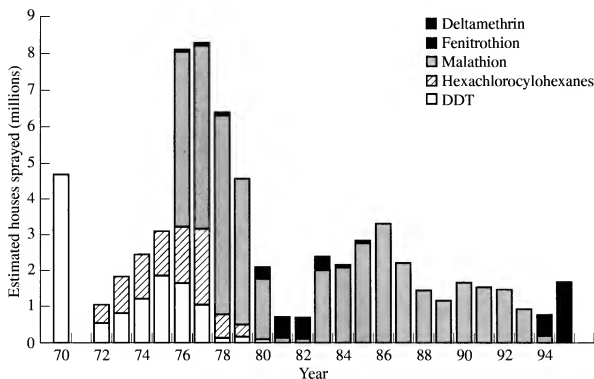


Fig. 5. Use of deltamethrin, fenitrothion, malathion, hexachlorocyclohexanes and DDT by the National Malaria Control Programme since 1970. To enable comparison between years, consumption in tonnes was converted to estimates of the numbers of houses sprayed, using a specific application rate for each insecticide and assuming a mean sprayable area per house of 250 m².

tinues to increase at the selected monitoring sites in Punjab and NWFP. For the most part, resistance exists as RI, and in some locations up to 60% of infections are still susceptible. Chloroquine continues to be useful against the latter and for the time being it remains the government-recommended first-line drug. Resistance to the second-line treatment, sulphadoxine-pyrimethamine, though present in Pakistan, is fairly rare (Rowland *et al.*, 1997a). Thus the treatment of falciparum malaria in Pakistan remains fairly straightforward and is not yet beset by the multi-drug-resistance problems that occur in South-east Asia (White, 1992).

A second trend to occur since the mid-1980s is a several-fold increase in the annual number of falciparum cases recorded in the Pakistani and Afghan refugee populations. Several factors have contributed to this. Although malaria in Pakistan, particularly falciparum malaria, is notoriously erratic (Zulueta *et al.*, 1980), climatic conditions do seem to have become more favourable for falciparum

transmission at the northern edge of its range. Bouma (1995) presented evidence for increasing rainfall in October and for a rise in November temperature in NWFP of 2°C over the last century. These factors would enhance transmission and prolong the transmission season. According to multivariate analysis, 82% of the recent inter-annual variation in falciparum in NWFP may be explained by rainfall in September and October, temperature in November and December, and humidity in December (Bouma, 1995).

Operational changes to the national MCP may have increased the number of cases detected. Active case detection by malaria control teams (a legacy of the eradication era) is gradually being phased out in Pakistan in favour of passive case detection. The number of government health posts diagnosing malaria has doubled over the last 15 years and this has doubled the number of slides collected by PCD. The case detection rate has less than doubled, however, because the shift to PCD was at the expense of ACD. PCD and ACD records since the mid-1980s both show an

increase in falciparum SPR and falciparum:vivax ratios. At best, programme reform can only partly explain the upsurge in falciparum.

Vector control though indoor spraying has had a major impact on malaria in Pakistan in the past. The epidemic in the Punjab in the mid-1970s, for example, coincided with the development of resistance in vectors to DDT and HCH (hexachlorocyclohexanes), and was finally brought under control by spray campaigns with malathion (see Figs 4 and 5; Zuleta *et al.*, 1980). However, during the upsurge in malaria in the mid-1980s, use of malathion by the national programme was actually increasing, suggesting that factors unrelated to vector-control operations were responsible for the upsurge. The evolution of malathion resistance has had only a minor role; although one of the primary vectors in Pakistan, *Anopheles stephensi* (Pervez and Shah, 1989), became widely resistant to malathion during the mid-1980s (Rathor *et al.*, 1985), recent evidence suggests that spray campaigns with malathion are still effective in controlling malaria in areas where vectors are malathion-resistant (Rowland *et al.*, 1997b). The area under insecticide coverage has decreased in recent years (Fig. 5) and this may have contributed to the persisting high levels of falciparum.

The advent and rapid spread of chloroquine resistance in the mid-1980s coincided with the initial falciparum upsurge and may have contributed to it in two ways. Firstly, recrudescence infections lead to patients making repeated visits to health posts. This can inflate the true incidence of new infections (e.g. by 66%, in the present sentinel village). Secondly, inadequately treated infections may

persist into the post-transmission period and enlarge the 'overwintering' parasite reservoir, leading to a rapid increase in new cases when transmission resumes. Evidence suggests that chloroquine resistance may have initiated the falciparum upsurge in the mid-1980s and now helps to maintain it.

Thus there are many factors potentially or actually contributing to the upsurge in falciparum. To quantify the contribution made by chloroquine resistance (or by any other biological or operational factor) would require the analysis of local data that are simply not available, such as those on local increases in falciparum incidence when chloroquine resistance first developed in an area, or when malathion spraying first became restricted (Scholtens *et al.*, 1990), or when local anophelines became resistant to malathion (Lewis, 1990). Despite the inadequacies in the data, the evidence from the UNHCR malaria-control programme is that campaigns of selective spraying with malathion and lambda-cyhalothrin have successfully reduced the incidence of falciparum to a tenth of former levels in the Afghan refugee population of Pakistan (Rowland *et al.*, 1994, 1997b; Bouma, 1995). Thus the upsurge in chloroquine-resistant falciparum malaria in Pakistan is by no means insurmountable.

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